Clinical Value of Iodine-123 Beta-Methyliodophenyl Pentadecanoic Acid (BMIPP) Myocardial Single Photon Emission Computed Tomography for Predicting Cardiac Death Among Patients With Chronic Heart Failure

Ryu Sasaki, MD; Isao Mitani, MD*; Takashi Usui, MD; Yutaka Kitamura, MD**; Yuzuru Yoshii, MD†; Toshiyuki Ishikawa, MD*; Kazuaki Uchino, MD*; Nobukazu Takahashi, MD*; Kazuo Kimura, MD*; Satoshi Umemura, MD*

In the present study, the effectiveness of $^{123}$I-β-methyliodophenyl pentadecanoic acid (BMIPP) single photon emission computed tomography (SPECT) for predicting cardiac death of patients with chronic heart failure was evaluated. Abnormalities of fatty acid metabolism are found in patients with chronic heart failure and BMIPP was developed as a tracer for scintigraphic assessment of myocardial fatty acid utilization. The study group comprised 74 patients with chronic heart failure with a left ventricular ejection fraction (LVEF) <45% on left ventriculography or radionuclide angiocardiography. They underwent both $^{201}$TI SPECT and BMIPP SPECT. The uptake of tracer was scored semiquantitatively from 0 (normal) to 4 (defect) in 20 segments and a total defect score (TDS) for all 20 segments was calculated. On planar images the mediastinum to heart count ratio (H/M) was calculated for the BMIPP and TI studies, and the H/M$^{123}$BMIPP:H/M$^{201}$TI (H/M$^{123}$BMIPP divided by H/M$^{201}$TI) was also calculated. The mean follow-up period was 660 days and there were 17 cases of cardiac death. Multivariate analysis identified H/M$^{123}$BMIPP:H/M$^{201}$TI (p<0.05) and LVEF (p<0.05) as independent predictors of cardiac death. Analysis of the myocardial metabolism by BMIPP SPECT can predict the high-risk patients with chronic heart failure.

(Circ J 2003; 67: 918–924)

Key Words: Fatty acid metabolism; Heart failure; Nuclear cardiology

Heart failure remains a major cause of disability and mortality, despite recent therapeutic advances, and heart transplantation is the treatment of choice for patients with severe heart failure who cannot utilize other therapeutic options. However, the supply of donor hearts does not meet demand, and most patients die before transplantation. It has therefore become necessary to distinguish low-risk from high-risk patients, in order to identify the recipients most likely to benefit from heart transplants and thereby efficiently allocate therapeutic resources.

Iodine-123-15-(p-iodophenyl)-3-(R,S) methylpentadecanoic acid (BMIPP), a β-methyl-branched fatty acid analogue, was developed as a tracer for assessing the fatty acid utilization of the myocardium by single photon emission computed tomography (SPECT)\(^1\)\(^-\)\(^6\). BMIPP does not undergo β-oxidation, the major pathway for fatty acid metabolism in myocytes, and is entrapped mainly in the triglyceride fraction of the cytosol of the myocytes for a prolonged period of time.

The fatty acid metabolism of the myocardium in the failing heart is still a controversial subject. Paolisso et al found increased fatty acid oxidation and decreased carbohydrate oxidation in mild stage heart failure\(^7\), whereas Recchia et al showed that during the decompensation period of pacing heart failure in dogs there is a switch in the myocardial substrate away from free fatty acid use to glucose. It is important to note that there may be different alterations in myocardial metabolism in response to heart failure that are dependent on the particular stage of the disease\(^9\).

Abnormalities of BMIPP SPECT have been shown to be a sensitive marker of severe myocardial damage in ischemic heart disease, idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy and valvular heart disease\(^{10-23}\) and it is possible that BMIPP SPECT may reveal the metabolic switch in the end-stage failing heart and so be useful in predicting cardiac death. On this basis, we investigated whether $^{123}$I BMIPP SPECT could be used clinically for risk stratification of patients with chronic heart failure.

Methods

Study Population
Seventy-six patients (22 women, 54 men; mean age, 65±
9 years) who had been admitted for congestive heart failure at least one time previously and fulfilled the following criteria entered the study: stable chronic heart failure for more than 6 months; a low left ventricular ejection fraction (LVEF <45%) on either equilibrium radionuclear angiography or left ventriculography; and no severe concomitant disease. Patients were ineligible if they had any of the following: acute myocardial infarction within the past 3 months, unstable angina, an indication for revascularization at study entry, or any other disease that might substantially shorten survival or impede participation in a long-term trial. Overall mortality was the end-point of this study.

The causes of heart failure were dilated cardiomyopathy (28 patients), ischemic heart disease (38), valvular heart disease (2), hypertrophic heart disease (2), hypertensive heart disease (2), amyloidosis (1), post-myocarditis (1), and doxorubicin cardiomyopathy (1).

We conducted additional analysis of the subgroups of patients with either ischemic (8 women, 30 men; mean age, 69±8 years) or non-ischemic heart disease (12 women, 24 men; mean age, 61±9 years).

**Study Protocol**

The protocol was approved by the ethics committee of Yokohama City University. Informed consent was obtained from all subjects.

**Data Acquisition**

A 10-min static image of the anterior chest was acquired with a general all-purpose collimator at 20 min after injection of 111 MBq of 123I BMIPP. The data were collected in 256×256 matrices. The equipment used at each hospital was as follows: GE Starcam 3000XCP gamma camera (Yokohama City University Hospital, Center A), GE Starcam 3000 (Yokosuka City Hospital, Center B) and Toshiba 9300A (Fujisawa City Hospital, Center C). SPECT data were acquired in the following ways: 180° rotation with 32 projections of 50 s/step (Center A), 180° rotation with 32 projections of 30 s/step (Center B), and 360° rotation with 60 projections of 30 s/step (Center C). The energy window was 159 keV±20%. The data were collected in 64×64 matrices. Butterworth and Ramp filters were used for reconstruction.

Thallium-201 (201Tl) cardiac imaging was also performed within 1 month of the BMIPP imaging, using a low-energy high-resolution collimator. Patients were given an intravenous injection of 111 MBq of 201Tl. Except for an energy window of 70 keV±20%, data acquisition conditions were similar to those described for 123I BMIPP.

The heart-to-mediastinal count ratio (H/M) was calculated from anterior planar images (Fig 1) for both the 123I BMIPP and 201Tl studies (H/M_{BMIPP} and H/M_{Tl}, respectively). The cardiac uptake ratio of BMIPP to thallium (H/MBMIPP : H/MTl) was also calculated. Regional tracer uptake was scored semiquantitatively from 0 (normal) to 4 (severe defect) for 20 segments of the left ventricle (Fig 2), and the sum of the defect scores for all segments was calculated to derive the total defect score (TDS).

**Other Clinical Evaluations**

Echocardiographic measurements were obtained according to standard recommendations.24 End-diastolic and end-systolic diameters were measured, and fractional shortening was calculated. Blood samples were obtained in the early morning after the subjects had rested in the supine position for 30 min. Plasma brain natriuretic peptide (BNP) concentrations (Shionoria BNP kit, Osaka, Japan) were determined by radioenzymatic assay.

**Patient Care and Follow-up**

At study entry, the patients were receiving medical treatment, such as angiotensin-converting enzyme inhibitors (64% of all patients), diuretics (86%), digitalis (44%), amiodarone (7%), and ß-blockers (22%). After the initial evaluation, all subjects were followed up at their referring institutions or by their primary physicians.

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**Table 1** Characteristics of the Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>Entire (n=51)</th>
<th>Center A (n=26)</th>
<th>Center B (n=10)</th>
<th>Center C (n=15)</th>
<th>p value (among centers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.1±10.9</td>
<td>61.7±10.7</td>
<td>57.2±15.2</td>
<td>69.3±5.5</td>
<td>NS</td>
</tr>
<tr>
<td>M/F</td>
<td>21/30</td>
<td>13/13</td>
<td>3/7</td>
<td>5/10</td>
<td>NS</td>
</tr>
<tr>
<td>H/MBMIPP</td>
<td>2.43±0.43</td>
<td>2.33±0.31</td>
<td>2.04±0.11</td>
<td>3.03±0.27</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>H/M_{Tl}</td>
<td>2.66±0.45</td>
<td>2.55±0.32</td>
<td>2.14±0.17</td>
<td>3.19±0.37</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>H/MBMIPP:H/M_{Tl}</td>
<td>0.95±0.12</td>
<td>0.93±0.14</td>
<td>0.96±0.07</td>
<td>0.97±0.14</td>
<td>NS</td>
</tr>
</tbody>
</table>
Validation of H/M Variability and H/MBMIPP:H/MTl Variability

In order to validate H/M variability and H/MBMIPP:H/MTl variability among normal subjects, we selected 51 patients (center A 26 patients, center B 10 patients and center C 15 patients: Table 1) without a significant perfusion defect on both 201Tl cardiac imaging and BMIPP imaging, or on normal echocardiography. None of them had a cardiac event for 1 year after scintigraphy.

Data Analysis and Statistics

The following variables were tested for their relation to outcome: H/MBMIPP, BMIPP TDS, H/MTl, TI TDS, H/MBMIPP:H/MTl, LVEF, New York Heart Association (NYHA) symptom classification, plasma BNP concentration, and echocardiographic end-diastolic diameter. To evaluate the prognostic value of these variables at baseline, patients alive at the end of the study (survivors) were compared with those who died during follow-up (non-survivors). Death from cardiac causes was defined as progressive heart failure or as sudden death occurring within 1 h of the onset of cardiac symptoms.

Stat-View™ software (HULINX Co, Ltd) was used for all statistical analyses. Single regression analysis was used to calculate slopes (regression coefficients). The clinical characteristics of survivors and non-survivors were compared with unpaired Student’s t tests and \( \chi^2 \) analysis. The clinical characteristics among centers were compared with the Tukey method and \( \chi^2 \) analysis. The Cox proportional hazards regression model was used for survival analysis. The relationship between survival and other variables was examined by the Kaplan-Meier method and log-rank test.

For all tests, \( p \) values of less than 0.05 were considered to indicate statistical significance. All variables are expressed as means ± standard deviation.

Results

Seventy-four patients (97%) were successfully followed up. The mean follow-up period was 660 days (54–1,659) and during the follow-up, 17 patients died from cardiac causes, including 3 cases of sudden death.
Laboratory and demographic data for the entire study group and the 2 subsets of patients (survivors and non-survivors) are shown in Table 2. In the non-survivors the NYHA class was worse and the BNP concentration higher than for survivors. The SPECT data from the 2 subsets are shown in Table 3. The TDS for both Tl and BMIPP SPECT was higher in the non-survivor group than in survivors, and the H/MBMIPP:H/MTl was lower in the non-survivor group than in the survivors.

Univariate analysis revealed that significant predictors of survival were BNP concentration, functional class, BMIPP TDS, Tl TDS, LVEF, and cardiac uptake ratio of (H/MBMIPP:H/MTl) (Table 4). We determined a threshold value of H/MBMIPP:H/MTl with the best compromise between sensitivity and specificity of the ROC curve, taking the average minus 2 standard deviations of H/MBMIPP:H/MTl in normal subjects into consideration. The threshold value of LVEF was also determined with a ROC curve. Previous studies have shown that the slope of increase in annual mortality rate as LVEF falls appears to be steeper at LVEF <0.25. We determined a threshold value of BNP because previous studies have reported lower mortality in patients with BNP >240–440 pg/ml.

Multivariate analysis indicated that H/MBMIPP:H/MTl (p<0.05) and LVEF (p<0.05) were the only significant predictors of survival. None of the other variables contributed significantly to survival (Table 5).

When additional analyses were performed in the subgroups of patients with either ischemic or non-ischemic heart disease, H/MBMIPP:H/MTl remained an important predictor of survival in both subgroups. In contrast, LVEF and BNP concentration did not contribute significantly to survival in patients with non-ischemic heart disease (Table 6).

When we changed the inclusion criteria to LVEF less than 40% or 30%, H/M BMIPP:H/MTl still remained as the predictor for survival, but LVEF did not contribute significantly (Table 7).

| Table 5 Predictors of Long-Term Cardiac Death by Multivariate Analysis |
|--------------------------|------------------|-------------------|
| Hazard ratio | Confidence interval | p value |
| H/MBMIPP:H/MTl <0.75 | 5.57 | 1.14–27.3 | 0.034 |
| LVEF (<25%) | 5.46 | 1.13–26.5 | 0.035 |

LVEF, left ventricular ejection fraction.

| Table 6 Multivariate Analysis of Patients With Either Ischemic or Non-Ischemic Heart Disease |
|---------------------------------------------|-------------------|-------------------|
| Ischemic (n=38) | Non-ischemic (n=36) |
| H/MBMIPP:H/MTl | 4.8±1.7/7.8 | <0.01 | 5.4/2.7/4.1 | 0.043 |
| LVEF (<25%) | 6.6/2.2/9.4 | <0.01 | 7.6/4.4/3.0 | NS |
| BNP (>400 pg/ml) | 4.9/1.9/2.7 | <0.01 | 4.9/3.6/1.9 | NS |

See Table 4 for abbreviations.

| Table 7 Multivariate Analysis of Patients With LVEF <40%, or 30% |
|---------------------------------------------|-------------------|-------------------|
| LVEF<40% (n=52) | LVEF<30% (n=32) |
| H/MBMIPP:H/MTl | 2.87±1.33/4.68 | 0.03 | 6.09±3.02/4.08 | 0.044 |

LVEF, left ventricular ejection fraction.

Fig 3. Kaplan-Meier analysis for occurrence of cardiac death. The survival rate was significantly less in patients with a low ejection fraction (EF) (<25%). Log-rank value = 7.84.

Fig 4. Kaplan-Meier analysis for occurrence of cardiac death. The survival rate was significantly less in patients with a low H/MBMIPP:H/MTl (<0.75). Log-rank value = 9.21. BMIPP, -methyliodophenyl pentadecanoic acid; H/M, heart to mediastinal count ratio; Tl, thallium.
When a threshold value of 25% was used to evaluate the accuracy of LVEF for predicting survival, the sensitivity was 47.1%, the specificity 78.9%, the positive predictive value 40%, and the negative predictive value 83.3%.

H/M\textsubscript{MBIPP}:H/M\textsubscript{Tl} was found to have a threshold value of 0.75 for the prediction of survival; lower values were associated with a poor outcome. Use of this value to predict survival yielded a sensitivity of 52.9%, a specificity of 82.7%, a positive predictive value of 47.4%, and a negative predictive value of 85.5%.

Survival curves based on a threshold value of 25% for LVEF and 0.75 for H/M\textsubscript{MBIPP}:H/M\textsubscript{Tl} clearly showed a significant difference in outcome (Figs 3, 4).

The ROC curve for H/M\textsubscript{MBIPP}:H/M\textsubscript{Tl} was situated clearly to the left relative to the LVEF curve (0.63<\textsubscript{1}<0.85, 0.48<\textsubscript{2}<0.75) (Fig 5).

In order to validate the importance of H/M\textsubscript{MBIPP} and H/M\textsubscript{Tl}, we also analyzed the data from normal subjects in 3 centers. H/M\textsubscript{MBIPP} and H/M\textsubscript{Tl} at Center A (2.33±0.31 and 2.55±0.32, respectively) were significantly lower than those at Center C (3.03±0.27, 3.19±0.37) (p<0.05), and were significantly higher than those at Center B (2.04±0.11, 2.14±0.17) (p<0.05). In contrast, H/M\textsubscript{MBIPP}:H/M\textsubscript{Tl} did not differ among the 3 centers (A: 0.93±0.14; B: 0.96±0.07; C: 0.97±0.14) (Fig 6).

**Discussion**

The major finding of our study is that H/M\textsubscript{MBIPP}:H/M\textsubscript{Tl} is closely related to survival in patients with chronic heart failure and appears to be the most accurate predictor of outcome among the clinical variables examined. This finding suggests that evaluation of fatty acid metabolism in viable cardiac muscle may help to predict the probability of death from cardiac causes. We consider H/M\textsubscript{MBIPP}:H/M\textsubscript{Tl} a useful index that can be used for patients with ischemic heart disease or hypertrophic cardiomyopathy with variable integrity of the myocardium. Previous studies have reported that BMIPP uptake is high in the patients with congestive heart failure and others have shown that fatty acid oxidation is increased in mild stage heart failure. It is important to note that there may be differential alterations in myocardial metabolism in response to heart failure that are dependent on the particular stage of the disease. The findings of our clinical study suggest that in end-stage heart failure patients there is a metabolic switch from fatty acid to glucose.

**Prognostic Value of H/M\textsubscript{MBIPP}:H/M\textsubscript{Tl} and LVEF**

Most invasive and noninvasive indicators of cardiac dysfunction strongly correlate with outcome. In particular, a decreased LVEF is closely associated with mortality in patients with either idiopathic cardiomyopathy or ischemia. Consistent with the results of previous studies, we found that LVEF was an independent predictor of death. Both LVEF and H/M\textsubscript{MBIPP}:H/M\textsubscript{Tl} had greater prognostic value than the other variables examined. When these 2 variables were compared in our study population, H/M\textsubscript{MBIPP}:H/M\textsubscript{Tl} was a better predictor of outcome than LVEF, irrespective of the method used for analysis. H/M\textsubscript{MBIPP}:H/M\textsubscript{Tl} that standardizes BMIPP cardiac uptake with Tl cardiac uptake is a useful index that can be used for patients with ischemic heart disease or hypertrophic cardiomyopathy with variable integrity of the myocardium.

**Subgroup Analysis**

Subgroup analyses between patients with ischemic and non-ischemic heart disease revealed several differences in the contribution of clinical characteristics to survival. In the patients with ischemic heart disease, H/M\textsubscript{MBIPP}:H/M\textsubscript{Tl}, LVEF, and BNP concentration were significant predictors of survival, but in those with non-ischemic heart disease LVEF and BNP concentration did not contribute significantly. The relationship between LVEF and survival varies depending on the characteristics of the study group and is strongest in patients who have had a myocardial infarction, including those with symptomatic congestive heart failure. A LVEF <0.30 has consistently been associated with increased mortality in patients who have congestive heart failure with ischemic heart disease. The relationship between LVEF and outcome in patients with dilated cardiomyopathy is less clear, but becomes more distinct in the presence of marked systolic dysfunction (LVEF <0.20). In the present study the LVEF was 32.3±8.0% in the patients with ischemic heart disease, as compared with 30.4±9.4%.
in those with non-ischemic heart disease. This difference in LVEF may underlie the distinct results in patients with ischemic heart disease and those with non-ischemic heart disease.

When we changed the inclusion criteria to LVEF less than 40% or 30%, H/MBIIPP:H/MTr still remained as the predictor for survival, which suggested that H/MBIIPP:H/MTr would be useful for risk stratification of patients with lower LVEF. In fact, when a threshold value of H/MBIIPP:H/MTr <0.75 was used in patients with a LVEF <25%, the ability of this value to predict survival yielded a sensitivity of 62.5%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 80%.

Study Limitations

The small number of subjects limited the value of subgroup analysis. In addition, the prognostic value of H/MBIIPP:H/MTr was compared with that of only a small number of echocardiographic and radiographic variables. Correlations between H/MBIIPP:H/MTr and other clinical variables, such as serum sodium concentration, exercise duration, and peak oxygen uptake on exercise testing, were not analyzed. Numerous studies have shown that 123I-metaiodo benzylguanidine imaging and peak oxygen uptake are useful for assessing prognosis in patients with heart failure. Whether H/MBIIPP:H/MTr will remain an independent predictor of outcome in a more complete multivariate model remains to be determined. The cost-effectiveness of this technique must be examined, too. Both 201Tl and 123I BMIPP imaging were necessary in our protocol, making the cost of the examination relatively expensive.

In our study, markedly decreased BMIPP uptake in severely ill patients precluded clinically meaningful tomographic imaging. The use of positron emission tomography (PET) tracer may overcome this limitation. Further study is necessary to evaluate whether PET analysis of myocardial fatty acid utilization is a more sophisticated technique for risk stratification in patients with chronic heart failure.

Conclusion

Our study results suggest that impaired fatty acid metabolism is a major determinant of mortality from either sudden death or progressive disease in patients with heart failure. A H/MBIIPP:H/MTr ratio of 0.75 or higher is significantly related to survival, and this relationship is stronger than that between LVEF and survival. Thus, myocardial metabolic analysis by BMIPP imaging is useful for identifying high-risk patients with chronic heart failure.

References


